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Research Article

THE STUDY OF ANTIHYPERLIPIDEMIC ACTIVITIES OF SCHIFF BASES OF 4(3H) QUINAZOLINONE DERIVATIVES IN RATS

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ABSTRACT

In the present study, the effects of subchronic treatments (6 weeks) of hypercholesterolemic rats with Schiff bases of 4(3H) Quinazoline at a sublethal dose level (200mg/Kg, p.o.) on antihyperlipidemic activity were investigated.

Atrovastatin, a hypolipidemic drug was used as a reference compound for data comparison. Treatment of rats with hypercholesterolemia with quinazoline compounds showed significant reduction in serum total cholesterol and serum triglyceride levels. The effect of two quinazoline derivatives and Atrovastatin on reduction of serum LDL-C level and other lipid parameters were studied. Results obtained from this study suggest that the antihyperlipidemic effect of quinazoline compounds were probably due to inhibition of dietary cholesterol absorption and also increase in the lipoprotein lipase activity.

Keywords: Quinazoline, Antihyperlipiemic activity, Schiff Bases

INTRODUCTION

Cardiovascular diseases are one of the major causes of death in all ethnic background. There are many causative factors for these diseases such as smoking, obesity, genetic background, diabetes mellitus and high blood pressure. High serum LDL-C and elevated total cholesterol levels are causes of atherosclerotic heart disease [1,2].

Hyperlipidemia is the presence of high levels of lipids in the blood. It is a metabolic derangement caused by many diseases, especially the cardiovascular diseases.

Elevated blood cholesterol level is due to abnormalities in the levels of lipoproteins. Lipoproteins carry cholesterol in the bloodstream. It may be caused due to diet, genetic factors like LDL mutations and by the presence of other diseases like underactive thyroid and Diabetes. The type of hypercholesterolemia depends on which type of particle (such as low density lipoprotein) is present in excess [3].

Atherosclerosis is a disease of blood vessels known colloquially as "hardening of the arteries".It is a progressive disease characterized by the accumulation of lipids and fibrous elements in the large arteries. It constitutes the single most important contributor to the growing cause of cardiovascular diseases [4].

There are many classes of lipid lowering agents. All of these drugs have different mechanisms of action. The effectiveness of these drugs depends on the lipid profile of the subject. These lipid lowering drugs possess various side effects. Thus, research is continuing to discover novel agents that are more potent and safe. The 4(3H)-quinazolinone derivatives are derivatives of the parent Quinazoline moiety. They are found to possess various biological activity such as anti-inflammatory [5, 6] anti-parkinsonian [7,8] ,anthelmintic [9],antibacterial [10], anticonvulsant [11] and hypotensive activities [12,13].

The antihyperlipidemic activities of quinazolinone derivatives are almost equal to that of β-sitosterol (a plant sterol of hypolipidemic activity) [1, 14].

The present work aims at investigating the antihyperlipidemic activities of 4 (3H) quinazolinone in hyperlipidemic rats.

Atrovastatin was adopted in this study as a reference hypolipidemic drug for data comparison [15].

MATERIALS AND METHODS

Synthesis

Preparation of 2-Phenyl benzoxazin-4-one A:

Anthranilic Acid was dissolved in pyridine. To this benzoyl chloride was added dropwise and cooled. The resulting mixture was stirred in room temperature for 2 hours. This was then poured in water containing 20% sodium bicarbonate solution. Solid product so formed was then filtered , dried and recrystallised from ethanol. M.P.121^{0}C. Both Anthranilic Acid and Benzoyl Chloride were taken in equimolar quantities.

Preparation of 2-Phenyl-3-amino quinazolin-4-3(H)-one B:

2-Phenyl benzoxazin-4-one was dissolved in ethanol. To this solution, Hydrazine Hydrate 80% was added in equimolar ratio. The resulting sample was refluxed for two and half hours. Then it was cooled. The product so formed was filtered, and recrystallised from ethanol. M.P.180^{0}C.

Preparation of Schiff bases of 2-Phenyl-3-(amino substituted arylidene) quinazoline-4 (3H)-ones C1 & C2:

The Schiff bases of 2-Phenyl-3-(amino substituted arylidene) quinazoline-4 (3H)-ones were prepared by triturating 2-phenyl-3-amino quinazoline compound with aromatic aldehydes namely salisaldehyde and vanillin at 80 ^{0}C to obtain 3-[{(2-Hydroxy Phenyl)-methylene}amino}-2-phenyl-quinazolin-4(3H)-one (C-1) and 3-[{(4-Hydroxy-3-methoxy phenyl) methylene} amino]-2-phenyl-quinazoline-4(3H)-one (C-2) respectively 16, 17. M.P. C-1 144^0 C and C-2 155 ^{0}C.The structures of the synthesized compounds were verified by IR, NMR and mass spectral analyses. The reaction can be summarized as follows in fig a.

Animals

Wister Albino adult male rats (150-200g) were used. The animals were kept on standard environmental conditions and feed on pellet diet and water was provided ad libitum.

Induction of hyperlipidemia was done. The animals were divided into 5 groups of 6 rats each and they received the following diets with or without treatment for 45 days orally[18-20].

Study Design

Group-I: Normal diet.

Group-II: Atherogenic diet containing 1% cholesterol and 3.8% sodium cholate suspended in coconut oil 5% once a day.

Group-III: Atherogenic diet + Atrovastatin (10mg/kg/day) suspended in Carboxy Methyl Cellulose (CMC) 1% once a day.

Group-IV: Atherogenic diet + C-1(200mg/kg/day) suspended in Carboxy Methyl Cellulose (CMC) 1% once a day.

Group-V: Atherogenic diet + C-2 (200mg/kg/day) suspended in Carboxy Methyl Cellulose (CMC) 1% once a day.

At the end of the treatment the rats were fasted overnight and blood samples were taken from the retro orbital venous plexus under light ether anesthesia using a glass capillary tube and immediately centrifuged to separate the Serum and stored at -20°C until lipid profile analysis 19.

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Anti hyperlipidemic activity was done to observe the effect of administration of C-1 and C-2 (200 mg/kg, p.o., once daily), Atrovastatin (10mg/kg, p.o, once daily) on serum lipid Parameter levels in rats treated with Atherosclerotic diet for 45days.

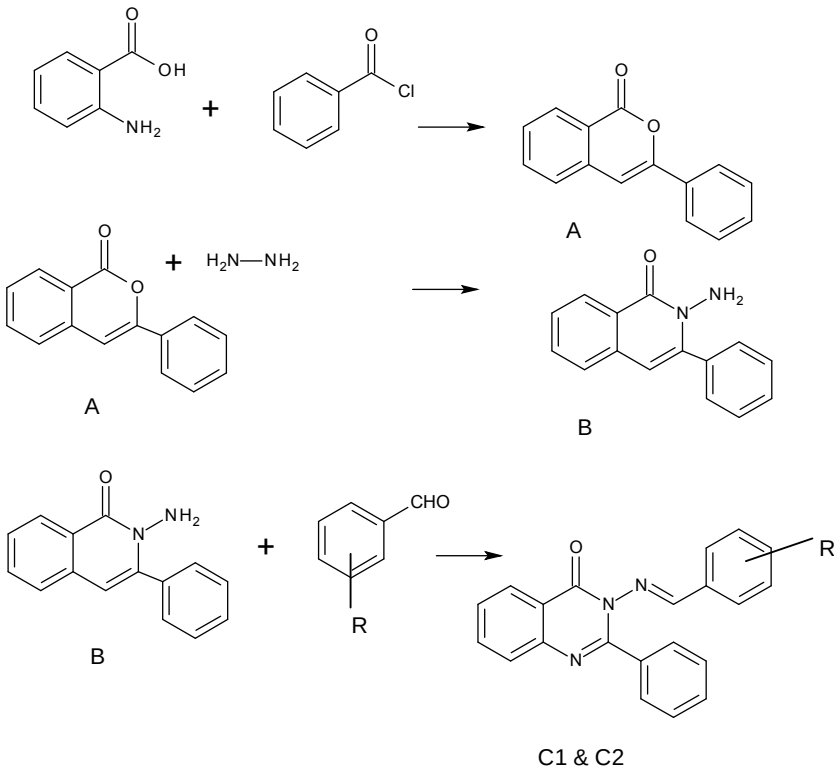

Fig. a:

R= C1 2-OH; C2 4-OH,3-OMe

Statistical Analysis

The data was analyzed using one way ANOVA followed by Tukey Kramer multiple comparison post test and the P value of 0.05 or less was considered significant.

RESULTS

Effect on serum total cholesterol (serum TC) level was studied. Here Rats treated with Atherosclerotic diet had serum TC level of (231.6±1.435mg/dl) when measured on day 45. This was significantly higher (P<0.01) when compared to serum TC levels in normal control rats (71.36±1.195mg/dl).

A.D rats treated with Atrovastatin (10mg/kg, p.o) had serum total cholesterol levels of 103.674± 0.574 where as C-1 and C-2 (200mg/kg, p.o., once daily) had serum TC level of 172.41±1.245mg/dl, 156.628 ± 1.392mg/dl when measured on day 45.This was significantly lower (P<0.01) when compared to the serum TC levels in A.D treated rats (231.6±1.435 mg/dl).

Effect on serum triglyceride (serum TG) level was studied. Here, Rats treated with Atherosclerotic diet had serum TG level of (237.4±1.060mg/dl) when measured on day 45. This was significantly higher (P<0.01) when compared to serum TG levels in normal control rats (149.825±0.730mg/dl).

A.D rats treated with Atrovastatin (10mg/kg,p.o) had serum TG levels of 54.407± 1.330 where as C-1 and C-2 (200mg/kg, p.o., once daily) had serum TG level of 93.63±1.292mg/dl, 76.94 ± 1.273mg/dl when measured on day 45.This was significantly lower (P<0.01) when compared to the serum TG levels in A.D treated rats (237.4±1.060 mg/dl).

Effect on serum HDL cholesterol (serum HDL-C) level was studied. The serum HDL-C levels in normal control rats were observed 50.66±0.88mg/dl. Rats treated with atherosclerotic diet had serum HDL-C level of 19.012±0.666mg/dl (P<0.01) when measured on day 45.

A.D rats treated with Atrovastatin (10mg/kg,p.o) had serum HDL-C levels of 62.05± O.80 where as C-1 and C-2 (200mg/kg, p.o., once daily) had serum HDL –C level of 60.01±0.67mg/dl,59.40 ± 0.45mg/dl when measured on day 45.

This was significantly lower (P<0.01) when compared to the serum HDL-C levels in A.D treated rats (19.01±0.66 mg/dl).

Effect on serum LDL cholesterol (serum LDL-C) level was studied. Here, Rats treated with Atherosclerotic diet had serum LDL-C level of (164.53±1.26mg/dl) when measured on day 45. This was significantly higher (P<0.01) when compared to serum LDL-C levels in normal control rats (180.66±0.88mg/dl).

A.D rats treated with Atrovastatin (10mg/kg,p.o) had serum LDL-C levels of 32.58± 1.09 where as C-1 and C-2 (200mg/kg, p.o., once daily) had serum LDL-C level of 91.10±0.97mg/dl,81.35 ± 0.81mg/dl when measured on day 45.This was significantly lower (P<0.01) when compared to the serum LDL-C levels in A.D treated rats (164.53±1.26 mg/dl).

Effect on serum VLDL cholesterol (serum VLDL-C) level was studied. Here, Rats treated with Atherosclerotic diet had serum VLDL-C level of (47.91±1.24mg/dl) when measured on day 45. This was significantly higher (P<0.01) when compared to serum VLDL-C levels in normal control rats (21.5±0.76mg/dl).

A.D rats treated with Atrovastatin (10mg/kg, p.o) had serum VLDL-C levels of 11.21± 0.77 where as C-1 and C-2 (200mg/kg, p.o., once daily) had serum VLDL-C level of 18.70±0.82mg/dl,17.04 ± 0.65mg/dl when measured on day 45.This was significantly lower (P<0.01) when compared to the serum VLDL-C levels in A.D treated rats (47.91±1.24 mg/dl).

Table 1: Effect of Atrovastatin, C-1 and C-2 on serum lipid parameters of atherogenic diet induced hyperlipidemic rats.

Groups	Treatment	Lipid parameters (mg/dl)				
		TC	TG	HDL –C	LDL-C	VLDL-C
I.	Normal	71.36 ±1.19	149.82 ±0.73	50.66 ±0.88	100.66 ±0.88	21.5 ±0.76
II.	Atherogenic Diet	231.6 ±1.43##	237.45 ±1.06##	19.01 ±0.66##	164.5 ±1.26##	47.91 ±1.24##
III.	Atherogenic Diet + Atrovastatin (10mg/kg)	103.6 ±0.57**	54.4 ±1.33**	62.05 ±0.80**	32.5 ±1.09**	11.21 ±0.77**
IV.	Atherogenic Diet + C-1 (200mg/kg)	172.4 ±1.24**	93.6 ±1.29**	60.01 ±0.67**	91.1 ±0.97**	18.7 ±0.82**
V.	Atherogenic Diet + C-2 (200mg/kg)	156.6 ±1.39**	76.94 ±1.27**	59.4 ±0.45**	81.3 ±0.81**	17.04 ±0.65**

Values are expressed as mean ± SEM for six animals in each group**p<0.01 considered statistically significant as compared to Group-III ,IV,V with Group-II. ##p<0.01 considered statistically significant as compared to Group-II with Group-I.

Table 2: Effect of Atrovastatin, C-1 and C-2 on Atherogenic Index and percentage of protection in various Groups of atherogenic diet induced hyperlipidemic rats.

Atherogenic Index and percentage of protection in various Groups			
Groups	Treatment	Atherogenic Index	Protection (%)
I	Normal	1.405 ± 0.011	-
II	A.D	12.25 ± 0.415##	-
III	A.D + Atrovastatin	1.668 ± 0.020**	86.300
IV	A.D + C-1	2.868 ± 0.030**	76.426
V	A.D + C-2	2.633 ± 0.024**	78.363

Values are expressed as mean ± SEM for six animals in each group.**p values < 0.01 when compared with group II. ##p values <0.01 when compared with group I.

DISCUSSIONS

The two synthesized products and has shown better antihyperlipidemic and antiatherosclerotic activity. It may be due to adjacent N atom at position3 and the functional groups (-OH, -OCH_3) on aromatic ring.Both the compounds possess hydroxyl group (-OH) in ortho position. C-2 has methoxy group (OMe) in Meta position.

The results revealed that feeding of atherogenic diet increased serum TC, TG, LDL-C, VLDL-C and decreased HDL-C level significantly over a period of 45 days (Table-1) when compared with normal lipid profile (p<0.0001).

Administration of 200mg/kg per day of Quinazoline derivatives of C-1 and C-2 showed significant decrease in TC(p<0.001), TG (p<0.001), LDL-C(p<0.001), VLDL-C (p<0.001) level and increase of HDL cholesterol(p<0.001) levels as compared to hyperlipidemic animals (Table-1). 200mg/kg, p.o. per day of Quinazoline derivatives of C-1 and C-2 treated animals showed decrease in the atherogenic index and increased percentage of protection. (Table-2)

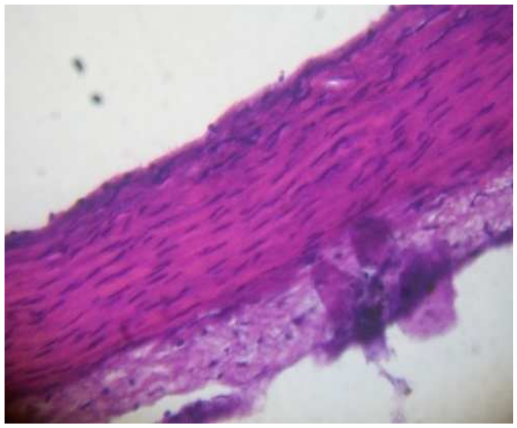

Fig. 1a: Normal (Group-I)

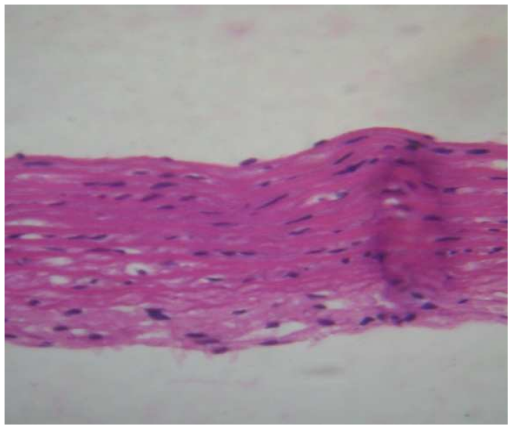

Fig. 1b: Atherogenic Diet (Group-II)

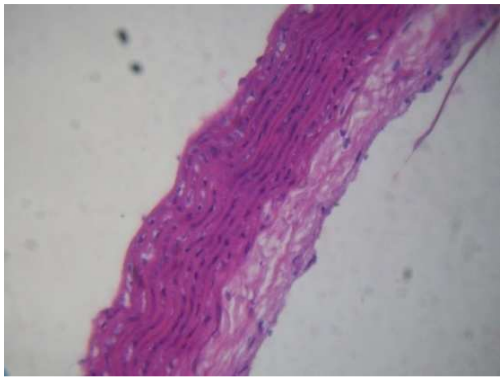

Fig. 1c: Atherogenic Diet + Atrovastatin (10mg/kg) (Group-III)

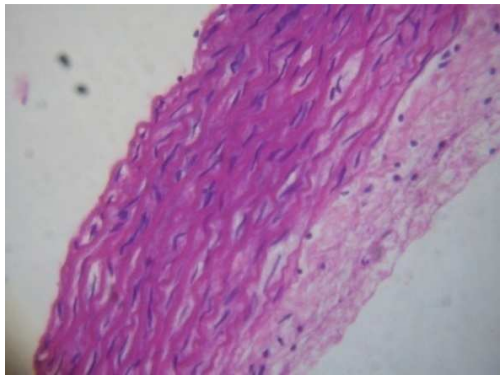

Fig. 1d: Atherogenic Diet + C- 1 (200mg/kg) (Group-IV)

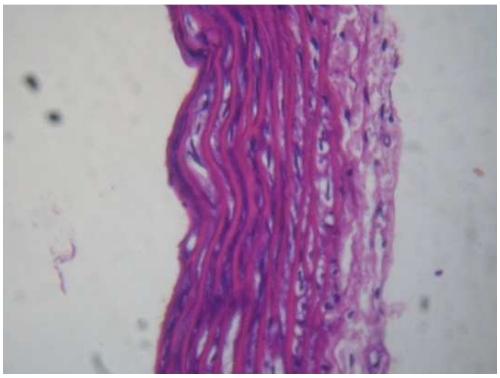

Fig. 1e: Atherogenic Diet + C-2 (200mg/kg) (Group-V)

Fig.1: Effect of atrovastatin, C-1 and C-2 on histopthological changes in rat artery.

It has been reported that many quinazoline compounds act possibly through inhibition of dietary cholesterol absorption and also increase in the lipoprotein lipase activity.

Hence, the antihyperlipidemic activity of compounds C-1 and C-2 probable due to the above mechanism.

Histopathological observations of artery

Histopathological observations of artery no atherosclerosis was found in Atherogenic control animals and in treated groups.

In Histopathological observations of artery, no atherosclerosis was found in atherogenic control animals and in treated groups.

It can be concluded from the present data that the level of serum TC,TG,LDL-C,VLDL-C which are actually raised in atherogenic control groups are lowered significantly with C-1 and C-2.

CONCLUSION

It can be concluded that Quinazoline derivatives C-1 and C-2 possess potential antihyperlipidemic activity. It is demonstrated by reduction in serum total cholesterol and LDL-C and increase in HDL-C level.

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